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ON THE ACTION OF NITRITE OF AMYL ON THE CIRCULATION.

BY

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ON THE ACTION OF NITRITE OF AMYL ON THE CIRCULATION.

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The property of causing flushing of the face and throbbing of the carotids, which nitrite of amyl possesses, was first observed by Guthrie in 1859, but no further notiee of it was taken till Dr. Richardson, in 1866, again drew attention to it. His experiments led him to conclude that it paralysed the nerves from the periphery to the centre, lessened the eontractility of the muscles, and dilated the capillaries in the web of the frog. They were shortly afterwards repeated by Drs. Gamgee and Rutherford, who, however, found no action on the nerves, either sensory or motor, and rarely any on the capillaries of the frog. In some other experiments, also unpublished, but whose result they have kindly communicated to me, they found that the sphygmographie tracing of the radial pulse undergoes a remarkable change, the waves becoming mueh more frequent and their ascent, but especially deseent, much more rapid; and the pulse-rate and pressure in a manometer connected with the carotid of a rabbit fall, when the vapour of the nitrite is inhaled. Previous division of the depressor nerves did not affect the result.

The diminished blood-pressure which it produces, led me to apply it in angina pectoris, and the good results I obtained made me anxious to investigate more closely the nature of its action. An excellent opportunity for doing so was afforded me by the kindness of Professor Ludwig, in whose laboratory at Leipzig the experiments, the result of which I am about to give, were earried on. With the exception of one or two on dogs, they were made upon rabbits; and instead of allowing the animals simply to inhale the vapour, artificial respiration was employed, thc apparatus being so arranged that the air could be either sent direct from the bellows, through a tube in the trachea, to the lungs, or passed

through a vessel containing the vapour of the nitrite. The advantages of this arrangement were that the bellows being worked by an engine with great regularity, the disturbing influences of unequal respiration on the blood-pressure were to a great extent avoided. One of the chief of these is that any strongly-smelling vapour, and nitrite of amyl among others, acting on the nose of rabbits, causes suspension of the respiration for a short time; and the alteration in the condition of the blood thus produced causes irritation of the vagus and slowing of the heart's action; such as Drs. Rutherford and Gamgee found accompanying the sinking of the blood-pressure in rabbits.

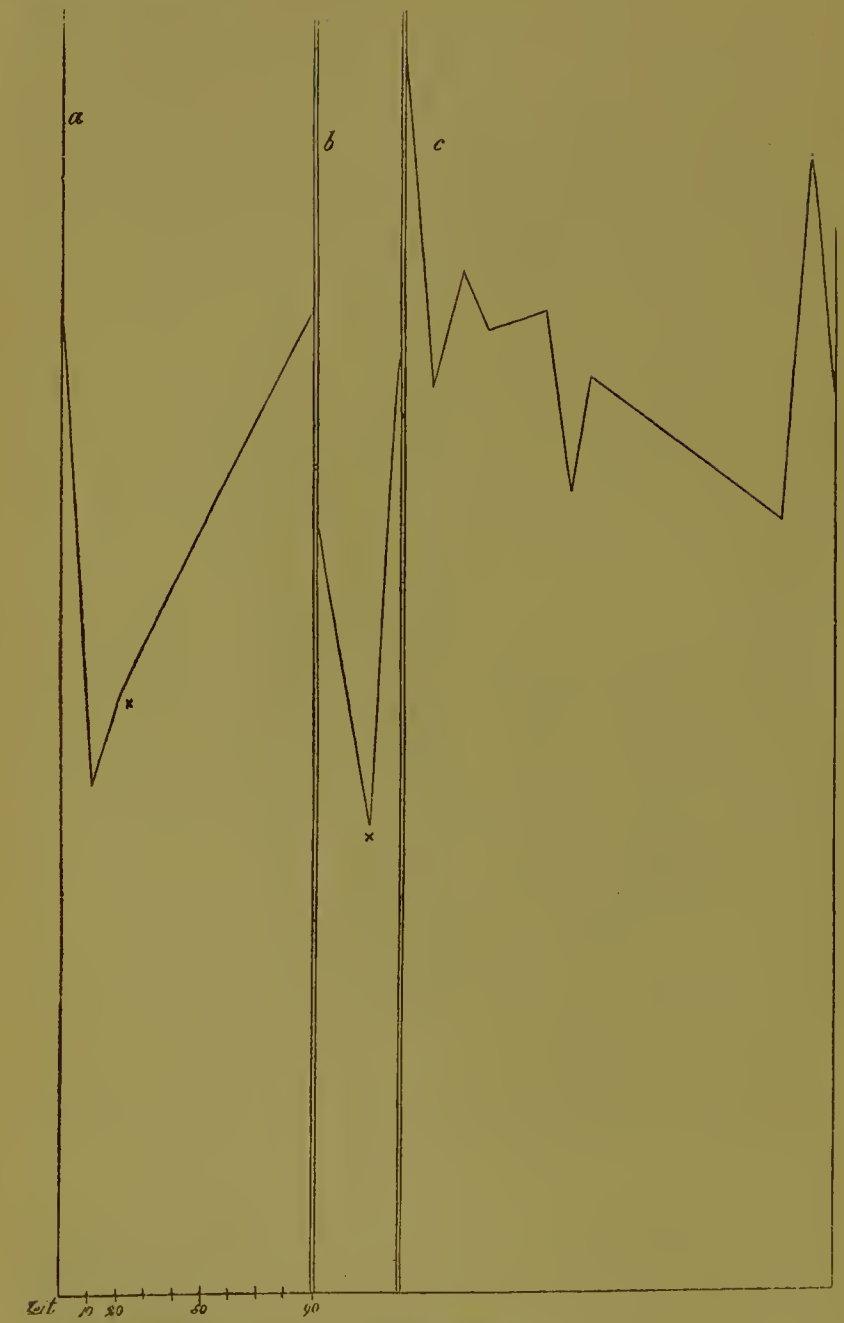
When air charged with the vapour was passed directly into the trachea of a rabbit the blood-pressure almost immediately sank very much, but the pulse-rate remained nearly unchanged. As the pressure sank general convulsions took place and the pressure immediately rose, notwithstanding the continued inhalation of the vapour, the pulse curves becoming at the same time indistinct, so that the rate could not be well ascertained.

When the vapour was discontinued after twenty seconds the pressure rose still more quickly, and in a minute at most attained its normal height, as is seen in Fig. 1, where the distance along the abscissa indicates the time and the ordinate the pressure in millimètres of mercury. This shows that very small quantities of the drug produce a great effect, and that its action speedily passes off, the vapour being either excreted or destroyed in the body.

In order to avoid the disturbance occasioned by the convulsions, the animals were then poisoned by curare and the vapour administered. The pressure, as before, sank immediately and did not return to the normal amount so long as the inhalation was continued. It did not, however, sink constantly and then remain at a definite minimum, but oscillated up and down, just as Traube observed it in curarised animals, and as is shown in the last two curves of Fig. 1.

It is possible that the convulsions which occur readily in rabbits, but which I have only once, and that to a very slight extent, seen in man, are suffocative, like those produced by CO, for Dr. Gamgee has shown that nitrites acting on the blood prevent hæmoglobin from giving up its O. This is the more probable as the respiration is first affected, and if a drop of nitrite of amyl be mixed with water and the vapour

FIG. 1


Pressure in mm. Hg.
a
b
c
Zero
20
40
60
Not poisoned.
Poisoned with curare.
× Inhalation stopped.
Seconds.

thus diluted be administered, the limbs remain quiet, but the animal begins to make respiratory movements independently of the bellows, and when the vapour is less diluted these become more and more marked till general convulsions take place.

The diminished blood-pressure might be due either to a lessened power of the heart, or a dilatation of the arteries and a consequently diminished resistance. That the latter is the true cause is rendered probable by the flushing which the vapour causes, both in the human face and the rabbit's ear, and is shown by what might at first seem an anomalous action in some dogs. When the pulse in dogs is slow, the inhalation of amyl produces comparatively little effect on the blood-pressure; and it might be thought that its action was different in them from rabbits, but the reason is that the pulse, which in rabbits is naturally rapid, and remains unchanged by the vapour, becomes in these dogs remarkably quick, almost as much so as in rabbits. If the vagi be first divided, so that the pulse in the dog becomes quick like that of the rabbit, and the nitrite be then inhaled, the pressure falls just as in rabbits. In order to confirm this view, and at the same time to decide the question, whether the dilatation of the vessels was due to a direct action of the substance upon them or to a diminution in the tone which the vaso-motor nerves derive from the medulla oblongata, another series of experiments was undertaken. This question was the more interesting from its connection with another research which I began under Professor Ludwig's direction, but unfortunately have not yet finished. Professor Ludwig observed, and directed my attention to the fact, that the alteration in the lumen of arteries noticed by Schiff, in the rabbit's ear, may be seen also in all exposed arterial twigs in the skin and connective tissue. They vary in amount and rapidity in different animals, and in the same animal at different times. They are sometimes absent, but in such cases may be generally produced by poisoning with curare, or by suspending the respiration; and when once aroused, they continue some time although the respiration be afterwards most carefully performed.

That these alterations are, at least in part, completely independent of the vaso-motor nerves in the brain is shown by their occurrence in the ear and other parts, after all the nerves, sympathetic and cerebrospinal, going to the part have been divided, and after division of the cord in

the neck notwithstanding the low pressure which then remains.

The form of the variation shows that they do not depend on varying blood-pressure in the large arteries; for sometimes a contraction suddenly appears between two parts of the artery filled with blood, and in one case in the rabbit's ear I noticed such a contraction take place in a small artery at the point where it branched off from a larger one, and proceed peristaltically downwards.

The lightest touch on an artery after division of the nerves causes a movement generally limited to the part, and consisting not in a contraction, but in dilatation, which remains for some time, and gradually disappears. As Gunning and Cohnheim have made similar observations on the tongue and web of the frog, and some facts in Sadler's research (Ludwig's 'Arbeiten,' 4th Jahrg.) can only be explained by an independent motion of the vascular walls, it seems to be a widely extended and therefore important phenomenon. If the nitrite acts through the vaso-motor centres in the brain, it should have no effect if these be separated from the vessels by dividing the cord in the neck, but if its action be exerted directly on the vessels, the division of the cord will not prevent it, and that it in fact does not do so, will be seen from Figs. 2 and 3. The blood-pressure, which had sunk very low after division of the cord, sank yet farther when the nitrite was inhaled. Although the sinking was not absolutely great, it was so relatively to the very low pressure already existing and was analogous to that observed on the section of a second splanchnic nerve after division of the first. The other experiments, to prove that the diminished blood-pressure after inhalation is due to dilatation of the vessels, and not to a weakened heart, consisted in compressing the aorta below the diaphragm and then administering the nitrite. If the diminution in pressure was due to a weakened heart, the inhalation of the nitrite should at once cause a diminution in the pressure to which the blood had attained after compression of the aorta. As only the circulation in the lower part of the body was in this way cut off, we cannot expect that no sinking should take place, but only that it should be less than the normal. In order to diminish the error from this source, these experiments were made after previous division of the cord in the neck so that the vessels should become relaxed, and the difference produced in their calibre by the vapour being thus less. The results obtained were

Fig. 2.

Uninjured.

Spinal cord destroyed at the axis.
× Inhalation stopped.

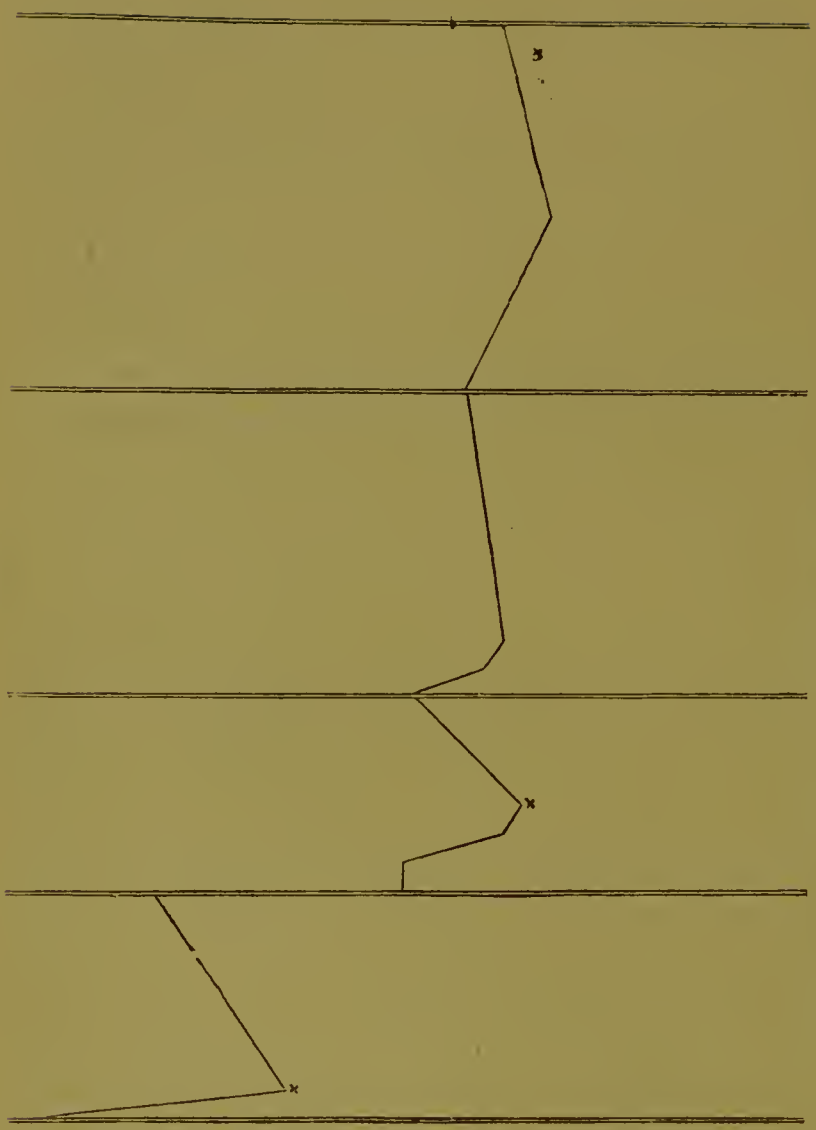


FIG. 3.

as shown in Figs. 4, 5 and 6, that sometimes a rise took place during the inhalation, but generally a sinking, much less, however, than in the normal condition.

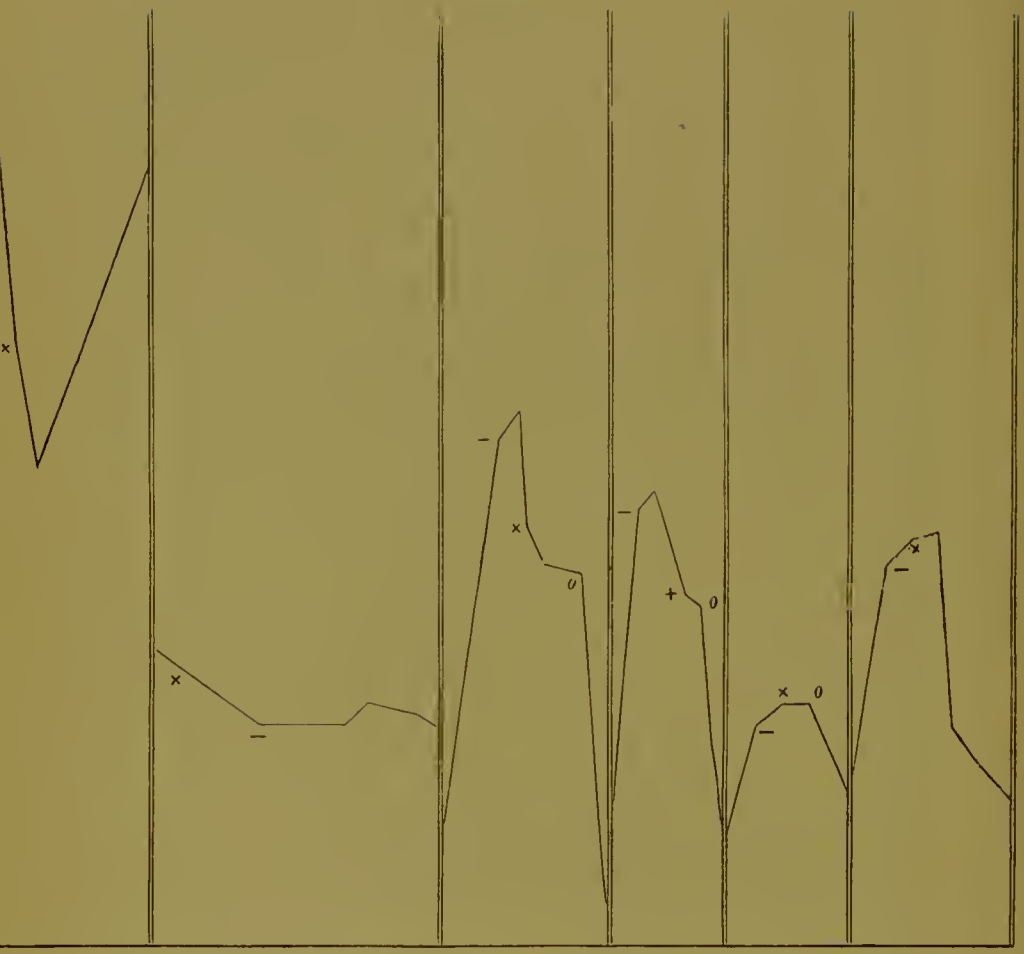
We may therefore conclude that the diminution in the blood-pressure is not due to weakening of the heart's action, but to a dilatation of the vessels, and that this depends on the action of the nitrite on the walls of the vessels themselves.

FIG. 4.

— Inhalation begun. × Inhalation stopped; at the beginning of the last three observations the aorta was compressed. o Aorta opened.

Whether this is due to its action on the muscular walls themselves, or the nerve-ends in them, cannot at present be with certainty said; and further experiments must be made to determine whether the walls of the arteries are the only structures consisting of unstriped muscle which are affected by it.

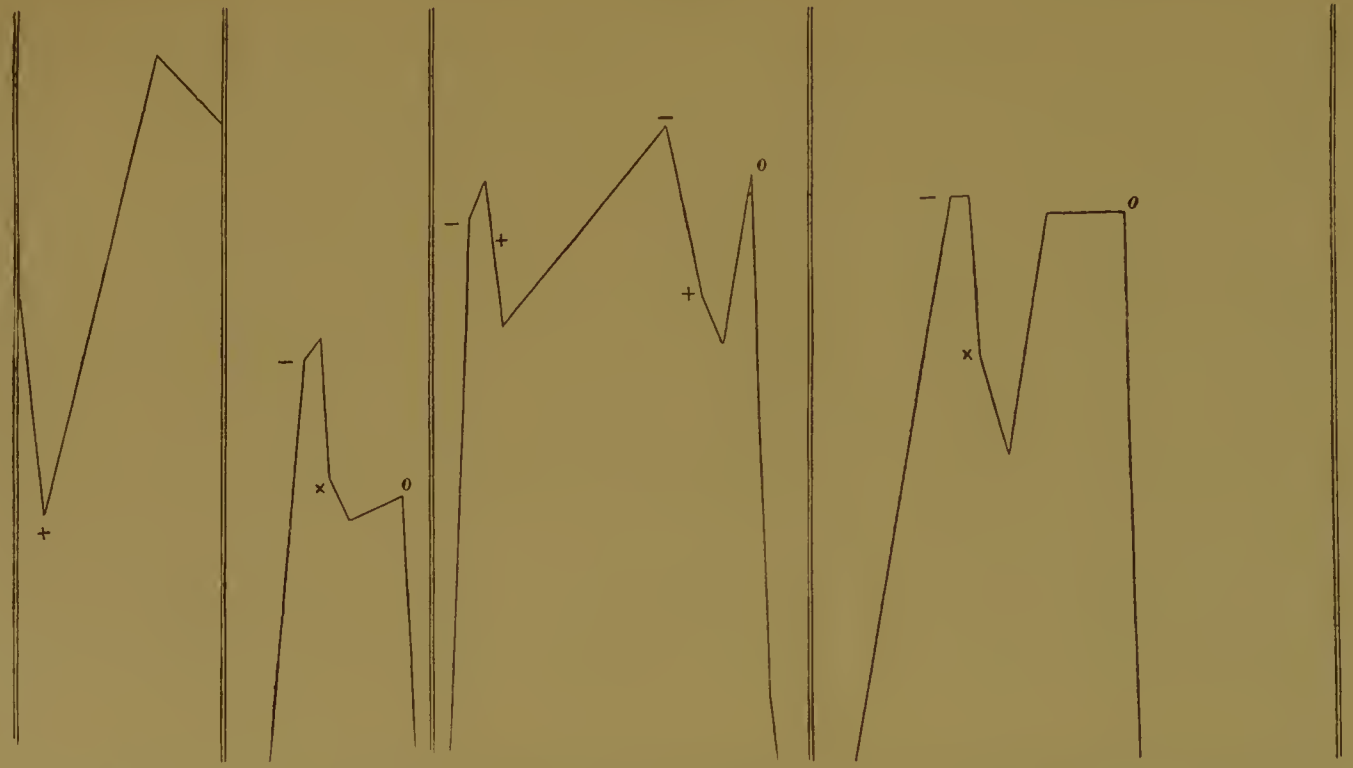
Fig. 5.



Cord cut in the neck.
In the last four observations the aorta was compressed; at *o* the aorta was opened
— Inhalation begun. + Inhalation stopped.

The further dilatation which takes place after the usual tone of the vessels has been destroyed by division of the cord, seems to indicate that it is of an active nature analogous to that in the vessels of the penis after irritation of its nerves; and this would point rather to an affection of the nerves than of the muscular fibres. In conclusion, I desire to express my warmest thanks to Professor Ludwig for the great kindness he has shown me, and for his invaluable advice and assistance in this investigation.

FIG. 6.



The ordinates indicating the pressure, begin 50 mm. above the abscissa. In the last three observations the spinal cord was divided; the aorta compressed, at *o* the aorta was opened. — Inhalation begun. + Inhalation stopped.

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